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Outcome of Conservative Therapy of Patients with Severe Intermittent Claudication

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Background. *Intermittent claudication due to peripheral artery disease (PAD) can be treated conservatively, or by revascularization.*
Objectives. *To assess the short-term outcome of conservatively-treated claudicants, and determine predictors for clinical improvement.*
Design. *A retrospective cohort study.*
Methods. *We evaluated Fontaine stage, walking distance and ankle brachial index (ABI) at baseline and after median 9 months (interquartile range (IQR) 6–24) in 181 patients with severe claudication.*
Results. *We found clinical improvement by at least one Fontaine stage in 38 patients (21%) with an increased walking distance from baseline median 100 m (IQR 50–150) to follow-up median 650 m (IQR 300 to unlimited;* $p < 0.001$*), but without changes in ABI (median 0.57, IQR 0.48–0.73 vs. median 0.54, IQR 0.45–0.81;* $p = 0.10$*). One hundred and thirty-eight patients (76%) remained clinically and hemodynamically stable. A worsening of the clinical stage but without amputation was recorded in five patients (3%). Female gender (hazard ratio (HR) 0.51,* $p = 0.052$*), diabetes (HR 0.35,* $p = 0.020$*), and baseline ABI below 0.44 (HR 0.31,* $p = 0.019$*) were associated with a reduced probability of clinical improvement.*
Conclusion. *Certain patients with intermittent claudication show substantial clinical improvement with conservative medical therapy, despite any lack of hemodynamic improvement. Given the low number of patients with clinical deterioration in the short term, primarily conservative therapy should be the preferred initial option for most claudicants.*

Key Words: Intermittent claudication; Conservative; Medical; Progression.

Introduction

Peripheral artery disease (PAD) is a serious medical problem in industrialized countries[1] and an indicator of systemic atherosclerosis. Symptomatic patients with intermittent claudication can be treated conservatively by risk factor modification and physical training,[2,3] or by revascularization.[4–6] Percutaneous balloon angioplasty and stenting are minimally-invasive procedures that have a high immediate success rate[4,7,8] and low rate of complications.[9,10] However, reocclusions after initially successful treatment frequently occur.[6,11–15]

Conservative or so-called 'best medical' treatment possess neither acute complications or immediate beneficial effects. Yet, exercise training, especially when supervised,[16] can lead to durable symptomatic improvement in patients with intermittent claudication[2,17–22] by substantially increasing the walking distance,[22] and favorably altering the cardiovascular risk factor profile.[2,3,23,24] However, the indications for interventional or conservative therapy are matter of an ongoing debate:[4,7,9,13,14,25] Randomized controlled trials[17,26] and meta-analyses suggest equal efficacy in the long-term. The TransAtlantic Intersociety Consensus (TASC) on the Management of Peripheral Artery Disease[6] and recent studies[14,27] recommend a primarily conservative approach for patients with claudication. Our retrospective cohort study was designed to analyze the short-term results of conservative therapy in patients with intermittent claudication, and to identify predictors of clinical improvement.

Material and Methods

Study design

We enrolled patients with PAD Fontaine stage IIb[6] (severe claudication with a maximum walking distance below 200 m) who attended our institutional

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out-patient ward from January 1997 to December 2002 and were recommended for primary conservative treatment at their initial presentation.

Patients

We screened more than 10 000 patients from our out-patient ward for the diagnosis of peripheral artery disease by review of original discharge letters and the out-patient ward database. Of all these patients with PAD Fontaine stage I (asymptomatic), IIa (walking distance above 200 m), III (ischemic rest pain) and IV (ischemic ulcers) were excluded. Furthermore, patients with previous or planned iliofemoral or femoropopliteal revascularization, either surgical or interventional, were excluded. In patients with bilateral disease, the clinically worse limb was considered for all analyses, each patient thus was included only once in the calculations. Thus, we identified 214 eligible patients with severe intermittent claudication Fontaine stage IIb at least of one lower limb. Thirty-three of 214 patients (15%) were excluded due to missing follow-up data, leaving 181 eligible patients. The median age of the study population was 71 years (IQR 60–76) and 92 patients (51%) were male. Demographic data and the clinical characteristics of the 181 patients are given in Table 1. Conservative treatment included risk factor modification and recommendations regarding physical training by systematic walking for at least 60 min daily. However, supervised physical training was not performed.

Table 1. Demographic data and clinical characteristics of the 181 patients with severe intermittent claudication (Fontaine stage IIb)

Risk factors	
Body mass index (kg/m^2)	27.1 (24.1–29.4)
Diabetes mellitus	69 (38%)
Arterial hypertension	129 (71%)
Hyperlipidemia	111 (61%)
Smoking	72 (40%)
Comorbidities	
Coronary artery disease (CCS stage)	
CCS I	47 (26%)
CCS II	24 (13%)
CCS III	4 (2%)
Carotid stenosis >25%	54 (30%)
Medication	
Acetyl salicyl acid (100 mg daily)	142 (79%)
Clopidogrel (75 mg (daily)	12 (7%)
Phenprocoumon	24 (13%)
Statins	69 (38%)
Peripheral artery disease	
Location of disease	
Aorto-iliac arteries	34 (19%)
Femoro-popliteal arteries	120 (66%)
Multivessel	27 (15%)
ABI affected limb	0.55 (0.44–0.69)
Maximum walking distance	100 (50–150)
ABI contralateral limb	0.77 (0.55–0.93)
Fontaine stage contralateral limb	
0	27 (15%)
I	9 (5%)
IIa	11 (6%)
IIb	134 (74%)

CCS denotes Canadian Cardiovascular Society.

Baseline data

We recorded the Fontaine stage,[6] walking distance (as reported by the patients), ankle brachial index (ABI) and arterial waveform (oscillography) of both limbs. In patients with significant mediasclerosis, defined as discrepancy between high ABI and low arterial waveforms, toe pressures at the first toe were obtained to calculate ABIs. Localization and length of the lesions were obtained by color-coded duplex sonography or magnetic resonance imaging (MRI). Because patients were routinely evaluated with serial non-invasive testing at our out-patients department, changes in the ABI and waveforms on pulse volume recordings (PVRs) were available for comparison with the symptomatic changes reported by the patients.

Definitions

Diabetes mellitus was defined according to the criteria of the American Diabetes Association and was assumed to be present in patients with a history of diabetes taking anti-diabetic medication. Arterial hypertension was diagnosed in patients with resting blood pressure values above 140/90 mmHg, and was assumed to be present in patients with a history of hypertension taking anti-hypertensive drugs. Coronary artery disease, according to the Canadian Cardiovascular Society (CCS) classification, was evaluated by treadmill exercise testing, dobutamin echocardiography, myocardial scintigraphy, and coronary angiography in selected cases.

Follow-up

Patients were followed by systematic chart review, and review of the original evaluation protocols. Routinely, patients were evaluated every 6 months with respect to clinical deterioration or improvement, including a physical examination and ABI and PVR measurements. However, patients were also advised to immediately attend the out-patient ward in case of worsening of the symptoms as indicated by reduced walking distance, rest pain or ulceration.

Study endpoints

The endpoint was the occurrence of clinical improvement or worsening of conservatively treated patients with severe intermittent claudication during follow-up, and the identification of factors associated with these clinical changes. The course of the clinical stage (changes were defined by at least one stage in the Fontaine classification), ABI, maximum walking distance, occurrence of critical limb ischemia, limb loss or need for emergency revascularization were outcome measures for evaluation of the primary study endpoint.

Statistical methods

Continuous data are given as the median and interquartile range (range from the 25th to the 75th percentile). Discrete data are presented as counts and percentages. We used Chi-square tests to compare groups of categorical data and to test for trends. Mann–Whitney U tests were applied to compare groups of unpaired continuous data and Wilcoxon paired tests used to analyze repeated measurements. Multivariate Cox proportional hazards models were used to assess factors associated with clinical improvement of PAD. The results of the Cox proportional hazards model are given as the hazard ratio (HR) and the 95% confidence interval (95% CI). Additionally, an ROC (receiver operator curve) analysis was applied to determine the best cut-off of ABI for predicting clinical failure of improvement. A two sided p-value <0.05 was considered statistically significant. Calculations were performed using MS Excel for Windows 2000, SPSS for Windows (Version 10.0, SPSS Inc., IL, USA) and Stata (release 8, Texas, USA).

Results

At baseline all 181 patients had Fontaine stage IIb. At the time of follow-up after median 9 months (IQR 6–24) 18 patients (10%) had become asymptomatic, 20 patients (11%) had Fontaine stage IIa (walking distance above 200 m), 138 patients (76%) had Fontaine stage IIb (walking distance below 200 m), four patients (2%) had Fontaine stage III (ischemic rest pain), and one patient (1%) had Fontaine stage 4 (ischemic ulcer). Overall, 38 patients (21%) showed a clinical improvement, 138 patients (76%) remained stable and a worsening of the clinical stage was recorded in five patients (3%). In none of the patients, was an amputation due to critical limb ischemia required during follow-up. Ipsilateral endovascular revascularisation was subsequently performed in 68 patients (37%) (67 patients with stable symptoms and one patient with clinical deterioration). Four patients (2%) with worsening symptoms underwent femoro-popliteal bypass surgery. The maximum walking distance was median 100 m (IQR 50–150) at baseline and median 100 m (IQR 50–200) at the time of follow-up ($p = 0.002$). Twenty-nine (42%) of 69 patients with diabetes had mediasclerosis as indicated by reduced arterial compressibility during ABI measurements. In these patients, toe arterial pressures instead of tibial artery measurements were obtained at baseline and follow-up. ABI remained widely unchanged with median 0.55 (IQR 0.44–0.69) at the affected limb at baseline and median 0.54 (IQR 0.41–0.70) at follow-up ($p = 0.39$). Walking distance and ABI of patients with clinical improvement, stable claudication and clinical deterioration by at least one Fontaine stage are given in Table 2. Remarkably, although the walking distance in patients with clinical improvement increased 6.5-fold, the ABI remained largely unchanged (Table 2).

We then performed a multivariate Cox proportional hazards analysis to determine factors independently associated with clinical improvement, and to adjust for possible confounding variables (Table 3). Female patients, patients with diabetes, and patients with a lower baseline ABI had a reduced probability of clinical improvement, adjusting for age (in tertiles), hypertension, smoking and location of the disease. Vice versa, male gender, non-diabetics as well as patients with higher ABI (above 0.44) were independent predictors of clinical improvement. Addressing the potentially best cut-off of ABI values for predicting failure of clinical improvement, ROC analysis and multivariate Cox models were applied revealing a best cut-off of 0.44 (Table 3).

Analyzing potential confounders for the association between gender and clinical improvement, we found that demographic data and clinical characteristics (as listed in Table 1) were equally balanced (all p-values >0.2) between male and female patients with exception to the frequency of current smokers (male 44/72; 49% vs. female 28/72; 32%; $p = 0.017$). However, testing for interaction between gender, smoking habits and clinical outcome by means of log likelihood ratio Chi-square tests we found no significant effect modification for a multiplicative interaction term (smoking * gender), suggesting that gender was associated with clinical outcome independent of smoking status.

We analyzed the potential effects of clopidogrel and statins with respect to clinical outcome as well as with

Table 2. Comparison of maximum walking distance and ABI in patients with clinical improvement, stable claudication and clinical deterioration by at least one Fontaine stage at baseline and after median 9 months follow-up (IQR 6–24)

	Baseline	Follow-up	*P*-value
Patients with stable claudication (n = 138)			
Walking distance	100 (50–150)	100 (50–150)	0.20
ABI	0.55 (0.44–0.68)	0.55 (0.41–0.70)	0.72
Patients with clinical improvement (n = 38)			
Walking distance	100 (50–150)	650 (300–∞)	<0.001
ABI	0.57 (0.48–0.73)	0.54 (0.45–0.81)	0.10
Patients with clinical deterioration (n = 5)			
Walking distance	50 (30–100)	–*	<0.001
ABI	0.46 (0.35–0.74)	0.33 (0.28–0.39)	0.03

Data are given as median and interquartile range (IQR: range from the 25th to the 75th percentile).
*Ischemic rest pain.

respect to changes in ABI but we did not find any significant association.

Discussion

We found a substantial symptomatic improvement in 21% of patients with initially severe claudication, although hemodynamic measurements remained widely unchanged. Female patients, diabetics, and patients with a lower ABI at study entry had a reduced probability for symptomatic improvement. Nevertheless, the rate of patients with worsening symptoms was low, and limb loss was not observed in this cohort of claudicants.

Our findings suggest that intermittent claudication can be considered as a life-style limiting condition rather than an immediate threat to limbs, confirming previous studies.[28,29] Claudicants therefore may be considered for conservative treatment including risk factor modification and physical training in the first instance. Revascularization can be offered as a secondary option in patients without or with insufficient improvement. Remarkably, the ABI even in patients with significant improvement of symptoms did not substantially change. One may speculate that the underlying causes that exert beneficial effects on walking distance may be an increased subjective tolerance of exercise-induced ischemic pain, improvement of the individual walking technique and optimization of cellular oxygen consumption (similar to the effects of training in athletes), factors which may be mutually not exclusive.

Table 3. Cox proportional hazards model to assess the probability of clinical improvement by at least one Fontaine stage

	Hazard ratio	95% Confidence interval	*P*-value
Female patients	0.51	0.25–1.00	0.052
Diabetes mellitus	0.35	0.15–0.87	0.020
ABI below 0.44	0.31	0.13–0.85	0.019

Adjusting for age (in tertiles), hypertension, smoking and location of atherosclerotic lesions (aortoiliac, femoropopliteal, multi-segment).

Female gender, diabetes mellitus, and lower baseline ABI were associated with a reduced probability of clinical improvement. Diabetes and lower ABI are well recognized as risk factors for progression of PAD[28,30,31] and frequently are associated with multi-vessel disease. Therefore, a reduced rate of clinical improvement in these patients is not unexpected. Although previously described,[28] it is less clear why women had a worse outcome. Nevertheless, it has to be acknowledged that female gender showed only a borderline significant association with outcome, leaving some uncertainty due to the small patient numbers.

Previous studies[4,26]showed no major difference in the outcome of conservatively or interventionally treated patients, (assessed by maximum walking distance and quality of life after a period of 2 years), with restenosis remaining the major limitation of angioplasty. Nevertheless, given the advanced age and the relatively high short-term mortality of patients with intermittent claudication,[32,33] symptomatic improvement even for only one or two years may justify interventional treatment in patients suffering from severe life-style limitations. Other studies,[34,35] suggest that claudicants who initially report only a small deterioration in quality of life have only a modest gain in quality of life by invasive therapy. Nevertheless, if severe symptoms and deterioration of quality of life are reported, revascularization should be considered.

We are aware of several limitations of this study. The documentation of walking distance as reported by the patients is debatable. Values at baseline and follow-up may be prone to reporting bias, a limitation which may be overcome by standardized walking tests or treadmill exercise testing, which unfortunately was not available in these patients. Objective testing of walking distance is particularly necessary for comparative studies between interventional and conservative therapy. Nevertheless, symptoms reported by the patients can be considered as the most important trigger for considering revascularization in claudicants. Our results therefore display data of immediate clinical relevance obtained in a real-life setting. In this study, the effect of 'best medical treatment' probably reflects the grade of patients' compliance in an unattended setting and may underestimate the effect of physical training. Other study limitations are a lack of data on patients' smoking status during follow-up

and the patients' compliance with regular physical training.

In conclusion, a significant proportion of patients with intermittent claudication improve substantially with conservative medical therapy, despite a lack of hemodynamic improvement. Given the low number of patients with clinical deterioration in the short term, primarily conservative therapy should be the preferred initial option for most claudicants.

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